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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/814,686	03/30/2004	M. Youssouf Badal	134.02US	8305

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EXAMINER	
JOYCE, CATHERINE	
ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/814,686	BADAL ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,12,16,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,12,16,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Amendment filed January 10, 2007 in response to the Office Action of July 12, 2006 is acknowledged and has been entered. Claims 6-11, 13-15, 17-20, and 23 are canceled, and claims 1-5, 12, 16, 21-22 are pending and are currently being examined.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 10/154042, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

Particularly claims 1-5, 12, 16, 21-22 are not supported by the prior-filed application because the disclosure of a method of determining disease status in a patient is not found in the prior filed application. If applicant disagrees with any rejection set forth in this office action based on examiner's determination that the claims are not entitled to the priority date of prior-filed application, Application No. 10/154042, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 1-5, 12, 16, 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5, 12, 16, 21-22 are indefinite because claims 1 and 16 are incomplete in that they omit essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a correlation step describing how the results of the assay relate back to the preamble of the method objectives. It is unclear what are the relative amounts of complex in the patient sample versus the amounts of complex amount in the reference sample and what status of disease it determines because there is no correlation step. Thus, the metes and bounds of the claims cannot be determined and one of skill in the art would not be apprised of the scope of the invention.

Claims 16 and 22 are indefinite in the recitation of the phrase "having a cleavage-inducing moiety with an effective proximity" and it is unclear what the cleavage-inducing moiety has an effective proximity to. Thus, the metes and bounds of the claims cannot be determined and one of skill in the art would not be apprised of the scope of the invention.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 3-5, 12, 16, and 21-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to the following:

A method of determining disease status of a patient suffering from a disease characterized by aberrant expression of one or more intracellular complexes, the method comprising the steps of:

Measuring directly in a patient sample an amount of each of one or more intracellular complexes;

Comparing each such amount to its corresponding amount in a reference sample; and

Correlating differences in the amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status of the patient (**claim 1**),

Wherein the patient sample is a fixed tissue sample (**claim 2**),

Wherein said one or more intracellular complexes is 14-3-3/BAD (**claim 3**),

Wherein the patient sample is a fixed tissue sample, Wherein said one or more intracellular complexes is 14-3-3/BAD (**claim 4**),

Wherein the patient sample is a fixed tissue sample, Wherein said one or more intracellular complexes is 14-3-3/BAD, wherein said disease is cancer (**claim 5**),

Wherein the patient sample is a fixed tissue sample, Wherein said one or more intracellular complexes is 14-3-3/BAD, wherein said disease is cancer, wherein said cancer is breast cancer (**claim 12**),

The method of claims 1, 2, 3, 4, 5 or 12 wherein each of said one or more intracellular complexes are determined by the steps of:

Contacting said one or more intracellular complexes in said patient sample with a cleaving probe having a cleavage-inducing moiety with an effective proximity, and with one or more binding compounds each having one or more molecular tags attached thereto by a cleavable linkage, the molecular tags of different binding compounds having different separation characteristics, such that the cleaving probe and the one or more binding compounds specifically bind to their respective intracellular complexes and the cleavable linkages of the one or more binding compounds within the effective proximity of the cleavage-inducing moiety are cleaved, thereby releasing one or more of the one or more molecular tags; and

Separating and identifying the release molecular tags to determine the presence or absence or the amount of said one or more intracellular complexes in said patient sample (**claim 16**),

And

A method of determining a status of cancer in a patient, the method comprising the steps of:

Simultaneously measuring in a sample from the patient amounts of at least one intracellular complex, wherein at least one intracellular complex comprises 14-3-3 protein and a BAD protein;

Comparing each such amount to its corresponding amount a reference sample; and

Correlating differences in the amounts from the patient sample and respective corresponding amounts from the reference sample to the disease status of the patient. (**claim 21**),

The method of claim 21 wherein said at least one intracellular complex is determined by the steps of:

Contacting said one or more intracellular complexes in said patient sample with a cleaving probe having a cleavage-inducing moiety with an effective proximity, and with one or more binding compounds each having one or more molecular tags attached thereto by a cleavable linkage, the molecular tags of different binding compounds having different separation characteristics, such that the cleaving probe and the one or more binding compounds specifically bind to their respective intracellular complexes and the cleavable linkages of the one or more binding compounds within the effective proximity of the cleavage-inducing moiety are cleaved, thereby releasing one or more of the one or more molecular tags; and

Separating and identifying the release molecular tags to determine the presence or absence or the amount of said one or more intracellular complexes in said patient sample (**claim 22**).

The specification contemplates the determination of disease status of a patient by measuring the amount of one or more intracellular complexes (page 3, lines 12-18),

wherein such complexes may be measured using reagent pairs that comprise a cleaving probe and a binding compound (page 3, lines 20-27). The specification further teaches that such intracellular complexes include 14-3-3/BAD (page 4, lines 9-10). The specification further teaches that disease status includes but is not limited to the features including likelihood of contracting a disease, presence or absence of a disease, prognosis of disease severity, and likelihood that a patient will respond to therapeutic treatment that acts through an intracellular complex (page 12, lines 3-10). The specification also teaches that status of disease includes cancer status (page 19, lines 24-26). The specification teaches an assay that may be used to measure the relative amounts of two complexes that contain the BAD protein: (i) 14-3-3 protein/BAD protein and (ii) Bcl-2 protein/BAD protein (Example 3).

The teaching of the specification cannot be reasonably extrapolated to enable the claims because one of skill in the art could not predict that the invention would function as claimed in "determining disease status of a patient suffering from disease" or "determining a status of a cancer in a patient". In particular, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to the use of detecting a BAD/14-3-3 complex to determine disease status, other cancers including breast cancer as contemplated and claimed. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence (abstract). Further, with regard to determining disease status that includes prognosis of disease severity or likelihood that a patient will respond to specific therapeutic treatment that acts through the intracellular complex, Tockman teaches that marker predictive value must be confirmed in prospective population trials (see abstract). Pertinent to the instant rejection, there is no evidence presented in the art of record that the detection of a BAD/14-3-3 complex may

be employed to determine any disease status, including any cancer status and there is no guidance in the specification, such as by way of working examples, that BAD/14-3-3 complex detection may be used to determine any disease status. Tockman goes on to teach that markers have clear biological plausibility and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). This irrefutable link between marker and acknowledged, in this case, disease status or cancer status is the essence of a valid marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated (p. 2716s, col 2).

Given that the art teaches that disease markers, i.e. cancer markers, must be validated, and given that the instant specification provides insufficient guidance to indicate a correlation between detection of the BAD/14-3-3 complex and any disease, such as by way of working examples, one of skill in the art could not predict that the invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Wildi et al. (2001, Gut 49:409-417).

The claims are drawn to the following:

A method of determining disease status of a patient suffering from a disease characterized by aberrant expression of one or more intracellular complexes, the method comprising the steps of:

Measuring directly in a patient sample an amount of each of one or more intracellular complexes;

Comparing each such amount to its corresponding amount in a reference sample; and

Correlating differences in the amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status of the patient (**claim 1**),

Wherein the patient sample is a fixed tissue sample (**claim 2**),

Wildi et al. teaches that inhibin βA forms homodimers to form activin A (page 3), and that the immunohistochemisty expression analysis of inhibin βA expression in colon cancer showed that only faint immunoreactivity for inhibin/activin βA was visible in stage I disease whereas stage IV disease exhibited strong inhibin/activin βA immunoreactivity (page 10, and Figure 7). Wildi et al. further teaches that these findings suggest that activin A (a homodimer of inhibin/activin βA) can serve as marker for advanced colorectal cancer (page 13). Thus, all of the claim limitations are met.

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8700.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Catherine M. Joyce
Examiner
Art Unit 1642

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